National Institute for Health and Care Excellence

Single Technology Appraisal (STA)
177Lu-PSMA-617 for treating PSMA-positive hormone-relapsed metastatic prostate cancer after 2 or more therapies [ID3840]

Response to consultee and commentator comments on the draft remit and draft scope (pre-referral)

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Advanced Accelerator Applications (AAA), A Novartis Company	Yes, this is an appropriate topic to refer to NICE for appraisal.	Comment noted. No action required.
	Bayer plc	No comment	Comment noted. No action required.
	Prostate Cancer UK	Yes, this is a highly appropriate new treatment for NICE to be considering based on the recent publication of its phase III trial and its opening up of a new treatment modality for advanced prostate cancer.	Comment noted. No action required.
	Welsh Health Specialised	No comment	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Services Committee		
Wording	Advanced Accelerator Applications (AAA), A Novartis Company	Yes, the wording of the remit is appropriate. However, androgen receptor directed therapy (ARDT)' should be updated to the preferred lexicon 'androgen receptor pathway inhibitor' for clarity.	Comment noted. The remit has been updated to 'to appraise the clinical and cost effectiveness of 177Lu-PSMA-617 within its marketing authorisation for treating previously treated prostate-specific membrane antigen (PSMA) positive, hormone-relapsed metastatic prostate cancer'. The exact specification of previous treatment and terminology will be in the marketing authorisation. The population section of the scope has been updated to refer to androgen receptor pathway inhibitor'

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	Bayer plc	No comment	Comment noted. No action required.
	Prostate Cancer UK	Wording is mostly appropriate but thought must be given to whether prior taxane chemotherapy should be mentioned – though this was an inclusion criterion in the VISION trial, the recent approval of enzalutamide in metastatic hormone-sensitive prostate cancer setting (mHSPC) and the alternative provision during the COVID pandemic mean that many patients will be coming through to end stage treatments for prostate cancer in years to come having not had taxane chemotherapy, whether or not they were suitable candidates for it at earlier disease stages. This is discussed further below and is a reasonable topic to consider during the appraisal, but should not be presumed within the remit.	Comment noted. The remit has been updated to 'to appraise the clinical and cost effectiveness of 177Lu-PSMA-617 within its marketing authorisation for treating previously treated prostate-specific membrane antigen (PSMA) positive, hormone-relapsed metastatic prostate cancer.' The exact specification of previous treatment and terminology will be in the marketing authorisation.
	Welsh Health Specialised Services Committee	No comment	Comment noted. No action required.

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Timing Issues	Advanced Accelerator Applications (AAA), A Novartis Company	The NHS should implement usage of the technology as close to marketing authorisation as is feasible within the NICE appraisal programme. Treatment decisions in later lines of hormone relapsed metastatic prostate cancer (also referred to as metastatic castration-resistant prostate cancer [mCRPC]), after docetaxel and an androgen receptor pathway inhibitor, are limited and typically driven by the toxicity profile of therapy, the fitness of patients for further treatment and patient or physician choice, especially in the case of chemotherapy. Despite the progress in treatment of advanced prostate cancer over the past decade, outcomes remain poor in patients with mCRPC. There remains an unmet need for additional therapeutic options in the mCRPC setting, particularly given the earlier use of androgen receptor pathway inhibitor and docetaxel due to treatment pathway evolution in the UK. VISION is the first Phase III clinical study demonstrating the value of targeted medicine for a broad population within mCRPC. Patients were eligible for inclusion into VISION if they had had prior treatment with an androgen receptor pathway inhibitor and at least one taxane-based chemotherapy. Patients were treated with either [177Lu]Lu-PSMA 617 (hereinafter 177Lu-PSMA-617) with standard of care (SOC) or SOC alone. VISION is also the first Phase III trial investigating a radioligand therapy and provides validation of a targeted approach to the treatment of advanced prostate cancer through the use of the PSMA molecule to target cancer cells. The trial design allowed for recruitment of patients with a large unmet need in the mCRPC space, and prior treatment of eligible patients matches UK clinical practice. With this in mind, AAA request that this appraisal be prioritised, considering the continued disease burden to mCRPC patients and benefit of 177Lu-	Comment noted. NICE aims to provide draft guidance to the NHS as close as possible to the date when the marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. No action required.

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		PSMA-617, in line with its anticipated MHRA marketing authorisation expected in [redacted].	
	Bayer plc	No comment	Comment noted. No action required.
	Prostate Cancer UK	There is significant clinical interest in this topic and we would consider it a matter of high priority within the prostate cancer community.	Comment noted. NICE aims to provide draft guidance to the NHS as close as possible to the date when the marketing authorisation for a technology is granted. NICE has scheduled this topic into its work programme. No action required.
	Welsh Health Specialised Services Committee	No comment	Comment noted. No action required.
Additional comments on the draft remit	Advanced Accelerator Applications (AAA), A Novartis Company	No further comments.	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Bayer plc	No comment	Comment noted. No action required.
	Prostate Cancer UK	No comment	Comment noted. No action required.
	Welsh Health Specialised Services Committee	No comment	Comment noted. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Advanced Accelerator Applications (AAA), A Novartis Company	To align with the proposed changes to the wording of the draft remit, all instances of the term 'ARDT' should be updated to the preferred lexicon 'androgen receptor pathway inhibitor'. To fully capture the burden of prostate cancer in the UK, it should be noted that prostate cancer is the most frequently diagnosed cancer in men in the UK.[1] Between 10% and 20% of prostate cancer cases develop castration-resistance within five years, and >50% of mCRPC patients die within three years.[2] Prostate cancer is the fifth leading cause of cancer death in men worldwide, causing more deaths than pancreatic cancer, rectal cancer, bladder cancer or leukaemia individually.[3] In the UK, prostate cancer is the second most common cause of cancer death in men, accounting for 13% of all cancer deaths in 2018 (11,890 deaths; age-standardised mortality of 45.9 per 100,000 males and 18.9 per 100,000 males and females).[1]	Comments noted. ARDT has been updated to androgen receptor pathway inhibitor. The background section aims to provide a brief summary of the disease and how it is managed, it is not designed to be exhaustive in its detail. No changes made.

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		Consider altering to the following wording to clarify the high level of expression of prostate-specific membrane antigen (PSMA) in patients with mCRPC: 'Prostate cancers can highly express a transmembrane protein called prostate-specific membrane antigen (PSMA)' Please update 'castrate-resistant' to 'castration-resistant' as this is the most commonly used lexicon in the literature. For clarity it should be noted that Radium-223 dichloride is recommended by NICE for treating hormone-relapsed prostate cancer with symptomatic bone metastases and no known visceral metastases in adults, only if they have already had docetaxel or if docetaxel is contraindicated or is not suitable for them.[4] References: 1. Cancer Research UK (2018) Prostate cancer mortality statistics. Available at: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer#heading-Zero. [Last accessed: June 2021]. 2. Nussbaum N, George DJ, Abernethy AP, et al. Patient experience in the treatment of metastatic castration-resistant prostate cancer: state of the science. Prostate Cancer Prostatic Dis 2016;19:111-21. 3. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394-424.	The third paragraph has been updated to 'Prostate cancers can highly express a transmembrane protein called prostate-specific membrane antigen (PSMA)' Castrate-resistant has been updated to castration resistant. It is noted that Radium-223 would only be a comparator in the population for which it is indicated. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		4. National Institute for Health and Care Excellence (NICE). Radium-223 dichloride for treating hormone-relapsed prostate cancer with bone metastases (TA412). Available at: https://www.nice.org.uk/guidance/ta412. [Last accessed: June 2021].	
	Bayer plc	No comment	Comment noted. No action required.
	Prostate Cancer UK	The background information does not include the recent approvals of darolutamide and enzalutamide in the non-metastatic hormone-relapsed and metastatic hormone-sensitive indications, respectively. By the time the appraisal officially starts there may also have been a recommendation for apalutamide, which is currently going through its own appraisal.	Comments noted. The scope has been updated to include the recommendations in technology appraisals 580, 660 and 712 respectively.
	Welsh Health Specialised Services Committee	No comment	Comment noted. No action required.
The technology/ intervention	Advanced Accelerator Applications (AAA), A Novartis Company	This section provides a comprehensive description of the technology, although the following points should be considered: ^{177}Lu-PSMA-617 is administered intravenously via methods that are deemed appropriate and safe by a nuclear medicine physician. This may include use of a syringe, syringe pump, gravity method, or vial with pump. Therefore, the wording in the scope should be updated to clarify that ^{177}Lu-PSMA-617 can be administered by intravenous infusion or injection.	Comment noted. The technology section aims to provide a brief summary of the technology and how it works. Additionally, the scope is written, as far as possible, using lay language. The scope

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		To provide additional clarity for a non-clinical audience, it is suggested that the explanation of the mechanism of action for ^{177}Lu-PSMA-617 is updated. The following wording is suggested: ^{177}Lu-PSMA-617 is a novel targeted therapy that consists of three distinct components: 1. An unstable lutetium isotope (^{177}Lu). This radioactive atom decays emitting a high energy beta particle which kills the cancer cells. 2. A ligand that binds specifically to PSMA expressed on the surface of PC cells. 3. A ligand which binds the PSMA-specific ligand to a cage housing the ^{177}Lu atom. PSMA is an actionable therapeutic and diagnostic target, expressed primarily on prostate cells at levels 100- to 1,000-fold greater than benign prostate tissues, Once bound to a prostate cancer cell, the ^{177}Lu isotope decays emitting a beta particle and delivering radiotherapy directly to cancerous cells.[1,2] Beta particles have a short path length (1.8 mm), allowing for precision delivery to the site of malignancy whilst limiting damage to surrounding tissues.[3] References: 1. Chang SS. Overview of prostate-specific membrane antigen. Reviews in urology 2004;6 Suppl 10:S13-S18. 2. Donin NM, Reiter RE. Why Targeting PSMA Is a Game Changer in the Management of Prostate Cancer. Journal of nuclear medicine : official publication, Society of Nuclear Medicine 2018;59:177-182. 3. Emmett L, Willowson K, Violet J, et al. Lutetium (177) PSMA radionuclide therapy for men with prostate cancer: a review of the	has been updated to state that Lu-PSMA can be administered by intravenous infusion or injection.

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		current literature and discussion of practical aspects of therapy. J Med Radiat Sci 2017;64:52-60.	
	Bayer plc	No comment	Comment noted. No action required.
	Prostate Cancer UK	This is accurate.	Comment noted. No action required.
	Welsh Health Specialised Services Committee	No comment	Comment noted. No action required.
Population	Advanced Accelerator Applications (AAA), A Novartis Company	The anticipated marketing authorisation for ^{177}Lu-PSMA-617 is: [redacted] The proposed population to be considered in this appraisal is therefore aligned to the anticipated marketing authorisation. The relevant patient subgroups which may be considered separately in this appraisal are: [redacted]	Comment noted. No action required.

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	Bayer plc	No comment	Comment noted. No action required.
	Prostate Cancer UK	As discussed above, the prior treatments in the history of late-stage metastatic prostate cancer patients are likely to change over the coming years. The recent approval of enzalutamide in the mHSPC setting will reduce the numbers having docetaxel as their first treatment. Though they could subsequently have taxane chemotherapy, evidence is unclear as to whether it has any benefit (in the ARCHES trial only 11 patients (23.9%) had docetaxel after enzalutamide, and 74 in ENZAMET (29.0%)). This raises uncertainty over whether prior taxane therapy should be necessary for eligibility for lutetium therapy. Further, the COVID pandemic has seen a significant interruption in the provision of docetaxel for metastatic hormone-sensitive prostate cancer meaning a population cohort will, in the next few years, be requiring late-stage treatment without having received chemotherapy. Finally, recent NICE appraisals have identified populations unsuitable for taxane chemotherapy. While the VISION trial required prior taxane chemotherapy, and thus does not provide evidence for a population without taxane exposure, the forthcoming PMSAfore trial is testing Lu-PSMA-617 against a second ARDT after initial ARDT failure in a population without prior chemotherapy. This should answer the question of whether prior chemotherapy is necessary for lutetium therapy, and therefore should be considered when setting the population definition for Lu-PSMA-617. The other aspect of the population definition presented here that is worth considering is “PSMA positive”. Different trials have used different definitions of PSMA positivity. The key Phase 3 trial in this appraisal, VISION, used a	Comments noted. It is anticipated that the marketing authorisation would specify the previous treatments required to be eligible for 177Lu-PSMA-617. No action required. The definition of PSMA positive will not be included here, because

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		relatively broad definition of at least one metastatic lesion of any size in any organ system with greater uptake of 68Ga-PSMA-11 than that of liver parenchyma, while not showing any lesions with PSMA uptake equal to or lower than that of liver parenchyma in any lymph node with a short axis of at least 2.5 cm, in any metastatic solid-organ lesions with a short axis of at least 1.0 cm, or in any metastatic bone lesion with a soft-tissue component of at least 1.0 cm in the short axis. Other trials have used different definitions and the suitability of these should be explored. If different definitions of PSMA positivity show greater predictive ability for outcomes on Lu-PSMA-617 therapy it may be beneficial to narrow down the population suitable for this treatment – this could also lead to a greater average overall survival benefit in this more tailored patient population. Some trials used specified Standardised Uptake Values on PET scans – this may make it easier to reduce inter-reader and inter-centre variation in interpreting PET scans for lutetium eligibility. We are awaiting the results of a retrospective analysis of the VISION data that will assess the predictive value of PSMA scans in relation to overall survival and radiographic progression free survival. If there is no relationship, and given that only 12.6% of patients tested with a Ga-PSMA scan in VISION did not meet the selection criteria, it would be worth discussion of whether the PSMA positivity criterion is necessary, as it may be that the PSMA scan adds expense and time to the procedure while serving no purpose. If a prior PSMA scan is shown to offer predictive information on treatment outcome, or is otherwise deemed necessary, it is worth considering which tracer and/or scanning technology should be used to demonstrate PSMA positivity. Most trials of Lu-PSMA-617 have used gallium-68-based PET-CT, frequently with the Ga-PMSA-11 tracer that is also a product of the company marketing Lu-PSMA-617. However, the reasons for use of this tracer are more logistical than scientific – it has been available at the centres taking part in trials, and has been available for the longest time of all PSMA imaging tracers. There are, however, other PSMA-based tracers available that could	it is anticipated it will be discussed by the appraisal committee during the development of the guidance. No action required. The population has been defined in the scope based on population included in VISION. Lu-PSMA-617 will be appraised within its marketing authorisation. The methods and costs of diagnostic testing are anticipated to be discussed during the appraisal.

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		provide a lot more flexibility for the NHS to offer Lu-PSMA-617 without any detriment to accuracy in determining PSMA positivity. Fluorine-18-based PSMA-targeting PET tracers are available and are in use across the UK. Though there is limited head-to-head trial evidence of non-inferiority to Ga-PSMA-PET, the available evidence does show that these tracers are generally equivalent in performance (see below for references). We are awaiting the results of a retrospective analysis of UK use of these tracers to further illustrate the comparison. The advantages of fluorine-based PET include a longer isotope half-life, much greater established manufacturing infrastructure, and greater scope for service expansion to meet increasing demand. Another alternative is a Tc-99m SPECT tracer targeting PSMA. SPECT-CT is a much more common and cheaper imaging technology than PET, available in the majority of UK hospitals to conduct bone scans. There is published evidence of 99mTc-PSMA SPECT being used to detect PSMA-positive metastatic prostate cancer. Though the sensitivity is lower than when using PET-CT, in the case of determining PSMA positivity prior to lutetium PSMA therapy this is of little importance. At this stage, the patient will have significant distributed disease, and the sensitivity to detect every metastatic lesion does not matter. The key is detecting PSMA-negative lesions, which is done with the anatomical scan, rather than the functional. The consequence of mandating a gallium PET-CT scan as part of an approval for this technology would be to, in effect, restrict its use in the UK. Patient access and outcomes, and minimising service variation, would be best served by allowing flexibility in PSMA scanning. The manufacturer of Lu-PSMA-617 has declared the treatment to be “isotope agnostic” in terms of its companion diagnostic scan, and NICE should take the same approach.	

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	Welsh Health Specialised Services Committee	No comment	Comment noted. No action required.
Comparators	Advanced Accelerator Applications (AAA), A Novartis Company	Given the limitations in available evidence, this appraisal should focus on NICE-approved medications suitable for patients with PSMA-positive mCRPC in patients previously treated with an androgen receptor pathway inhibitor and taxane-based therapy. Based on this, the comparator which should be considered relevant to this appraisal is SOC. **Docetaxel** Retreatment with docetaxel within the mCRPC pathway is possible according to NICE guidelines, however, docetaxel use earlier in the treatment pathway for advanced prostate cancer is current practice, as noted in NICE Guideline NG131, which states "off-label use of docetaxel in people diagnosed with hormone-sensitive metastatic prostate cancer is current practice".[1] NICE also note that the recommendations do not cover high-risk, non-metastatic prostate cancer, however, the use in this population may increase as well.[1] This is further supported by the NHS clinical commissioning policy statement for docetaxel in combination with androgen deprivation therapy for the treatment of hormone naive metastatic prostate cancer, which allows for commissioning of docetaxel for off-label usage in hormone naive metastatic prostate cancer.[2] The use of docetaxel prior to mCRPC can also be inferred from the National Prostate Cancer Audit which reports an increase from 27% to 36% this year in receipt of primary docetaxel by newly-presenting hormone-naive metastatic patients.[3]	Comments noted. **Docetaxel** The scope includes all possible comparators. The company can propose to exclude comparators in its evidence submission. The most appropriate comparator will be discussed by the appraisal committee during the development of this appraisal. No action required. **Radium-233** It is noted that Radium-

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		From systematic literature reviews, no evidence has been identified to support the use of docetaxel in mCRPC after disease progression on an androgen receptor pathway inhibitor, which limits the ability to conduct an indirect comparison. **Radium-233** Radium-223 is recommended by NICE as a treatment option for patients with symptomatic bone metastases and no known visceral metastases, who have already received a docetaxel treatment.[4] Comparisons between ^{177}Lu-PSMA-617 and radium-223, in patients for whom docetaxel is not suitable is further limited by the fact that no published RCTs for radium-223 for treatment of patients after progression on an androgen receptor pathway inhibitor. It should also be noted that radium-223 is primarily used to palliate pain and improve disease-related quality of life, rather than to extend survival.[5] **Olaparib** Olaparib has not received a Final Appraisal Document (FAD) through the NICE single technology appraisal process and is not used routinely in the NHS, nor is it established as current best practice. A further barrier to routine use in the NHS is the need for confirmation of a deleterious or suspected deleterious homologous recombination repair (HRR) gene mutation (either germline or tumour) before olaparib treatment is initiated.[6] Currently the NHS does not routinely test for germline BRCA1/2 mutations in prostate cancer patients, with somatic testing having been only recently included in the National Genomic Test Directory for Cancer. This provides a potential barrier due to new measures likely being delayed due to COVID-19, historical samples for testing potentially being unavailable or inappropriate due to concerns of genetic changes over time, and the invasiveness of the	223 would only be a comparator in the population for which it is indicated. The company can propose to exclude comparators in its evidence submission. The most appropriate comparator will be discussed by the appraisal committee during the development of this appraisal. No action required. **Olaparib** Olaparib has been removed as a potential comparator in the scope. The timelines for the ongoing appraisal of olaparib have changed meaning that the guidance for olaparib will be issued later than originally anticipated.

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		procedure potentially limiting additional biopsies to establish BRAC1/2 mutations for eligibility for treatment with olaparib. **Cabazitaxel** The VISION trial and the expected indication are in the post-taxane mCRPC setting.[7] NICE TA391 recommends cabazitaxel in combination with prednisone for patients with hormone-relapsed prostate cancer who have progressed during or after docetaxel, if the patient has an ECOG performance status of 0 or 1, the patient has had 225 mg/m^2 or more of docetaxel, and the treatment with cabazitaxel is stopped when disease progresses or after a maximum of 10 cycles.[8] The treatment and use of cabazitaxel in second and third line mCRPC is limited, with docetaxel use also being limited in mCRPC due to patient choice and NHS guidance released in June 2021 relating to the COVID-19 pandemic, which suggest a shift away from in-hospital treatments.[9] In addition, although the TheraP trial compares ^{177}Lu-PSMA-617 with cabazitaxel, this study is only powered for reduction in PSA and not for OS or rPFS.[10] Furthermore, TheraP only includes monotherapy treatment, and the study uses ^{177}Lu-PSMA-617 generated at the treatment centre (i.e., "homebrew") rather than AAA-provided drug.[10] Finally, clinical trials for cabazitaxel have substantial heterogeneity with the VISION trial due to the time lapse between studies, with VISION patients representing a frailer patient population, and VISION patients having all had prior taxane-based therapy, leading to difficulties in comparing outcomes across trials.[10] References: 1. National Institute for Health and Care Excellence (NICE). Prostate cancer: diagnosis and management (NG131). Available at:	**Cabazitaxel** The scope includes all possible comparators. The company can propose to exclude comparators in its evidence submission. The most appropriate comparator will be discussed by the appraisal committee during the development of this appraisal. No action required.

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		https://www.nice.org.uk/guidance/ng131. [Last accessed: June 2021]. 2. NHS England. Clinical Commissioning Policy Statement: Docetaxel in combination with androgen deprivation therapy for the treatment of hormone naïve metastatic prostate cancer. Available at: https://www.england.nhs.uk/wp-content/uploads/2016/01/b15psa-docetaxel-policy-statement.pdf. [Last accessed: July 2021]. 3. National Prostate Cancer Audit. Annual report 2020. Available at: https://www.npca.org.uk/content/uploads/2021/01/NPCA-Annual-Report-2020_Final_140121.pdf [Last accessed: June 2021]. 4. National Institute for Health and Care Excellence (NICE). Radium-223 dichloride for treating hormone-relapsed prostate cancer with bone metastases (TA412). Available at: https://www.nice.org.uk/guidance/ta412. [Last accessed: June 2021]. 5. Jiang XY, Atkinson S, Pearson R, et al. Optimising Radium 223 Therapy for Metastatic Castration-Resistant Prostate Cancer -5-year Real-World Outcome: Focusing on Treatment Sequence and Quality of Life. Clin Oncol (R Coll Radiol) 2020;32:e177-e187. 6. NHS England. National Genomic Test Directory. Available at: https://www.england.nhs.uk/publication/national-genomic-test-directories/. [Last accessed: July 2021]. 7. Sartor O, de Bono J, Chi KN, et al. Lutetium-177–PSMA-617 for Metastatic Castration-Resistant Prostate Cancer. New England Journal of Medicine 2021. 8. National Institute for Health and Care Excellence (NICE). Cabazitaxel for hormone-relapsed metastatic prostate cancer treated with docetaxel (TA391). Available at:	

Section	Consultee/ Commentator	Comments [sic]	Action
		https://www.nice.org.uk/guidance/ta391. [Last accessed: July 2021]. 9. NHS England. Interim treatment options during the COVID-19 pandemic. Available at: https://www.nice.org.uk/guidance/ng161/resources/interim-treatment-change-options-during-the-covid19-pandemic-endorsed-by-nhs-england-pdf-8715724381. [Last accessed: July 2021]. 10. Hofman MS, Emmett L, Sandhu S, et al. [¹⁷⁷Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial. The Lancet 2021;397:797-804.	
	Bayer plc	The sequencing and combination of available therapeutic options is an increasingly important topic as more treatment options become available. We suggest excluding radium-223 as a potential comparator because 177Lu-PSMA-617 is expected to be used later in the treatment pathway relative to radium-223. Indeed, a recent publication suggests that prior treatment with radium-223 may have a positive impact on OS, with patients treated with radium-223 prior to 177Lu-PSMA-617 showing a longer OS in all subgroups.1 Therefore, it seems highly likely that radium-223 will be used prior to 177Ls-PSMA-617 in the treatment pathway, which makes it an inappropriate comparator. Radium-223 has demonstrated significant efficacy before and after docetaxel both in clinical trials and through its extensive use in the real world setting across the world – it has also been prescribed and reimbursed in the UK in the pre-chemo setting as an interim option during COVID-19 due to the increased risk of myelosuppression associated with docetaxel. On the other	It is noted that Radium-223 and docetaxel would only be a comparator in the population for which it is indicated. The company can propose to exclude comparators in its evidence submission. The most appropriate comparator will be discussed by the appraisal committee during the development

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		hand, 177Lu-PSMA-617 has been investigated in VISION in patients with highly advanced disease more heavily pre-treated – all patients had progressed on at least one taxane (with roughly 40% progressing on two taxanes) and 17.4% of patients had also received prior radium-223 in VISION within at least 6 months prior to randomization. The comparator standard of care arm in VISION specifically excluded chemotherapy and radium-223, whereas following the discontinuation of the randomised treatment in VISION, patients were generally re-challenged with chemo or radiotherapy, with extremely few patients being administered subsequent radium-223. Preliminary data on overall survival and duration of therapy from REASSURE1 suggests the feasibility of 177Lu-PSMA-617 use subsequent to radium-223. Further data on the sequential use of radium-223 and 177Lu-PSMA-617 will be available from the RaLu study, a retrospective medical chart review to describe the safety of treatment with Lu-177 PSMA ligand therapy in mCRPC patient who had been previously treated with Ra-223 (estimated primary completion Q2 2022). We also suggest excluding docetaxel as a potential comparator in patients that had docetaxel at an earlier stage of the disease because the use of docetaxel at an earlier stage is not licensed and potentially not reflective of the previous docetaxel use in VISION. Moreover, the regimen of the early off-license docetaxel use that is currently commissioned in the UK (i.e. up to 6 cycles) differs from the licensed regimen in mCRPC (i.e. up to 10 cycles). References: 1. Sartor AO, la Fougère C, Essler M, Ezziddin S, Kramer G, Elllinger J, Nordquist L, Sylvester J, Paganelli G, Peer A, Bögemann M. Lutetium-177–prostate-specific membrane antigen ligand following radium-223 treatment in men with bone-metastatic castration-resistant prostate	of this appraisal. No action required.

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		cancer: real-world clinical experience. Journal of Nuclear Medicine. 2021 Jun 1.	
	Prostate Cancer UK	The potential comparators listed in the scope are more extensive than those we feel are appropriate for this appraisal. Cabazitaxel and best supportive care represent the true options for patients at this stage of the disease pathway. Lu-PSMA-617 was tested against cabazitaxel in the TheraP trial. Radium-223 is a suitable comparator at this stage of the pathway, but only for a subset of the patients who would be eligible for Lu-PSMA-617. The majority of patients in the VISION trial had bone metastases (91.5%), however 21.4% of patients had visceral metastases, meaning they would be contraindicated for Ra-223. In order to treat Ra-223 as a comparator, NICE must consider the sub-population with only bone metastases. This would require extracting data from VISION only for these patients, and would limit the other trials of Lu-PSMA-617 that could provide evidence. Patients in the VISION trial were not tested for BRCA1/2 mutations, therefore there is no evidence with which to compare lutetium therapy and olaparib. Rechallenge with docetaxel is possible for those who have completed six cycles, with up to a further four cycles potentially given. However, due to their overall health and/or the cumulative side effects of docetaxel treatments, not all patients will be able to tolerate this rechallenge with docetaxel and very few will reach the full ten cycles. Further, Lu-PSMA-617 would available after the docetaxel rechallenge cycles had been completed, at which point further docetaxel is not an option. Therefore, this is an inappropriate comparator. Patients in this situation would, if fit enough to tolerate it, progress onto cabazitaxel.	It is noted that Radium-223 would only be a comparator in the population for which it is indicated. The scope includes all possible comparators. The company can propose to exclude comparators in its evidence submission. The most appropriate comparator will be discussed by the appraisal committee during the development of this appraisal. No action required.
	Welsh Health Specialised	No comment	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Services Committee		
Outcomes	Advanced Accelerator Applications (AAA), A Novartis Company	The outcomes measures presented capture the most important health-related benefits of the intervention. Additional secondary outcomes from VISION will be presented in the company submission, but these outcomes are not expected to inform indirect treatment comparisons (ITC) or health economic modelling.	Comment noted. No action required.
	Bayer plc	No comment	Comment noted. No action required.
	Prostate Cancer UK	These outcomes are appropriate.	Comment noted. No action required.
	Welsh Health Specialised Services Committee	No comment	Comment noted. No action required.
Economic analysis	Advanced Accelerator Applications (AAA), A Novartis Company	An economic analysis that addresses the requirements of the NICE reference case will be submitted. A ten-year time horizon will be implemented, and the NHS and PSS perspective will be chosen.	Comment noted. No action required.
	Bayer plc	The cost of PSMA expression testing should be factored into the analysis.	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Prostate Cancer UK	The economic analysis scope is appropriate.	Comment noted. No action required.
	Welsh Health Specialised Services Committee	No comment	Comment noted. No action required.
Equality and Diversity	Advanced Accelerator Applications (AAA), A Novartis Company	There are a limited number of clinical centres which would be able to assess patients for PMSA positivity using PET/CT scanning and deliver 177Lu-PSMA-617. This may result in inequality due to the need for some patients to travel long distances to receive treatment.	Comment noted. Equality and diversity will be considered by the appraisal committee when formulating its recommendations. In addition potential health inequalities relating to access to services and treatment is anticipated to be discussed during the appraisal. The company will have the opportunity to provide evidence of equality and diversity in the submission. No action required.
	Bayer plc	No comment	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Prostate Cancer UK	As considered in other NICE appraisals for metastatic prostate cancer, older patients are more likely to be unsuitable to receive taxane chemotherapy. If chemotherapy is therefore an eligibility requirement for Lu-PSMA-617, there is the risk of indirect discrimination based on age as older men would be prevented from accessing this treatment.	Comment noted. The appraisal committee will discuss equality and diversity. No action required.
	Welsh Health Specialised Services Committee	No comment	Comment noted. No action required.
Other considerations	Advanced Accelerator Applications (AAA), A Novartis Company	No further issues.	Comment noted. No action required.
	Bayer plc	No comment	Comment noted. No action required.
	Prostate Cancer UK	No comment	Comment noted. No action required.
	Welsh Health Specialised Services Committee	No comment	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
Innovation	Advanced Accelerator Applications (AAA), A Novartis Company	^{177}Lu-PSMA-617 has an innovative mechanism of action and if approved will represent the first and only PMSA-targeted radioligand therapy for patients with PSMA-positive mCRPC. In general, patients in this population have a short life expectancy and substantially impaired quality of life.[1,2] Patients may also have experienced treatment cycling through various rounds of taxane and androgen receptor pathway inhibitor therapy, and hence a treatment with a novel mechanism of action is able to offer new hope to these patients. In recognition of the serious nature of mCRPC, and the potential for ^{177}Lu-PSMA-617 to offer a substantial improvement over currently available treatments, the US Food and Drug Administration (FDA) has granted a breakthrough therapy designation to ^{177}Lu-PSMA-617.[3] References: 1. Cancer Research UK (2018) Prostate cancer mortality statistics. Available at: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer#heading-Zero. [Last accessed: June 2021]. 2. Lloyd AJ, Kerr C, Penton J, et al. Health-Related Quality of Life and Health Utilities in Metastatic Castrate-Resistant Prostate Cancer: A Survey Capturing Experiences from a Diverse Sample of UK Patients. Value Health 2015;18:1152-7 3. Novartis Press Release. Novartis receives FDA Breakthrough Therapy designation for investigational 177Lu-PSMA-617 in patients with metastatic castration-resistant prostate cancer (mCRPC). Available at: https://www.novartis.com/news/novartis-receives-fda-breakthrough-therapy-designation-investigational-	Comment noted. Innovation will be considered by the appraisal committee when formulating its recommendations. The company will have the opportunity to provide evidence of the innovative nature of its product in the submission. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		177lu-psma-617-patients-metastatic-castration-resistant-prostate-cancer-mcrpc. [Last accessed: June 2021].	
	Bayer plc	No comment	Comment noted. No action required.
	Prostate Cancer UK	Yes, this is the first targeted radioligand therapy for metastatic prostate cancer. This innovation opens up a whole new class of treatments targeted to prostate cancer cells and independent of the androgen receptor mechanism. This presents a new avenue to tackle metastatic prostate cancer, which will be built on in the future. We consider this a step-change in prostate cancer treatment.	Comment noted. The appraisal committee will discuss the potentially innovative nature of this technology. No action required.
	Welsh Health Specialised Services Committee	No comment	Comment noted. No action required.
Questions for consultation	Advanced Accelerator Applications (AAA), A Novartis Company	Responses to the additional consultation questions are provided below. **Is prostate specific membrane antigen expression currently tested in UK clinical practice? How will people with PSMA-positive hormone relapsed metastatic prostate cancer be identified in clinical practice?** PSMA positron emission tomography–computed tomography (PET/CT) scanning represents a highly sensitive and accurate method for the staging of prostate cancer metastases, and is currently being used in selected NHS centres for patients who require more accurate staging of disease than can be achieved with bone scanning and magnetic resonance imaging (MRI).	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		Currently ^{68}Ga PET/CT scanning is accessible in five cities in England, and the diagnostic molecule ^{68}Ga-PSMA-11 will offer an additional option for imaging at these centres. A commercial version of ^{68}Ga-PSMA-11 has been approved by the FDA for imaging of PSMA-positive lesions in patients with suspected prostate cancer metastasis who are potentially curable by surgery or radiation therapy and therefore is anticipated to become the SoC for diagnosis and staging in patients with advanced prostate cancer.[1] A MHRA marketing authorisation [redacted] application for the AAA product ^{68}Ga-PSMA-11 is expected to be submitted in [redacted]. Furthermore, a ^{99m}Tc-labelled PSMA radiotracer is currently in development. This radiotracer is for use with single photon emission computed tomography–computed tomography (SPECT/CT) scanning.[2,3] Expansion of the existing service has been addressed through the NHS Levelling Up agenda and the company eagerly anticipate the future expansion of PET/CT facilities. It is also anticipated the commercialisation of ^{18}F fluorinated PSMA radiotracers for use with PET/CT infrastructure, and ^{99m}Tc-PSMA radiotracers for use with SPECT/CT infrastructure, will provide further options for the identification of suitable patients. **Is there a cut-off threshold of PSMA expression for being PSMA-positive?** In the VISION trial, patients must be ^{68}Ga-PSMA-11 PET/CT scan positive, as determined by the sponsor's central reader. The presence of PSMA-positive lesions was defined as ^{68}Ga-PSMA-11 uptake greater than that of liver	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		parenchyma in one or more metastatic lesions of any size in any organ system.[4] **Have all relevant comparators for ^{177}Lu-PSMA-617 been included in the scope?** Please see comments in the 'comparators' row above. **Which treatments are considered to be established clinical practice in the NHS for hormone relapsed metastatic prostate cancer previously treated with androgen receptor directed therapy (ARDT) and taxane based chemotherapy?** In patients with mCRPC previously treated with androgen receptor pathway inhibitor; treatment options remain limited. Established clinical practice for patients after disease progression on docetaxel and an androgen receptor pathway inhibitor is cabazitaxel or SOC, with limitations also highlighted in the "Comparators" section. Although NICE guidelines still recommend docetaxel post-androgen receptor pathway inhibitor, in practice, docetaxel is now predominantly used earlier in the treatment pathway. This is supported by a recent 2020 National Prostate Cancer Audit, which found that 36% of UK patients with newly diagnosed hormone-naïve metastatic disease receive docetaxel (with androgen-deprivation therapy [ADT]) as upfront therapy, furthermore, given that docetaxel was only added to the NICE guidelines as a treatment option for newly diagnosed hormone-naïve metastatic disease in 2019, it is expected that this proportion of patients in this population receiving docetaxel will continue to increase.[5]	Comment noted. No action required. Comment noted. See comparators section. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		Olaparib is currently undergoing NICE appraisal for previously treated, hormone-relapsed metastatic prostate cancer with homologous recombination repair gene mutations, but is currently not reimbursed in the UK and therefore does not represent established practice.[6] As mentioned above, olaparib is only suitable for prostate cancer patients with BRCA1/2 mutations, and this makes ITC of ^{177}Lu-PSMA-617 challenging as BRCA1/2 mutations were not captured in VISION.[4] **How should best supportive care be defined?** Combinations of the following treatments can be considered to constitute SOC for patients with mCRPC as per the VISION trial: • Supportive measures (pain medication, hydration, transfusions, etc.), and ketoconazole. • Hormonal agents (single or combinations), oestrogens including diethylstilbestrol (DES) and estradiol are allowed on study. • Luteinizing hormone-releasing hormone (LHRH) analogue for testosterone suppression including both agonists and antagonists. • Any corticosteroid such as dexamethasone, prednisone, etc. and 5-alpha reductases including finasteride and dutasteride • Abiraterone, enzalutamide, apalutamide or any other androgen receptor pathway inhibitor • Radiation in any external beam or seeded form is allowed on the study. This can include stereotactic body radiation therapy (SBRT) or palliative external beam or radiation involving seeds but not systemic radiopharmaceuticals • Bone targeted agents including zoledronic acid, denosumab and any bisphosphonates	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		What treatments used in UK clinical practice are classed as androgen receptor directed therapies? Abiraterone and enzalutamide are the androgen receptor pathway inhibitors which are indicated for the treatment of mCRPC and are used in UK clinical practice. Apalutamide and darolutamide are also androgen receptor directed therapies which have ongoing trials and NICE appraisals for earlier use within the prostate cancer pathway (e.g., mHSPC, nmCRPC). **Is it appropriate to exclude abiraterone and enzalutamide as potential comparators because patients can only receive them once in UK clinical practice and it is expected that ^{177}Lu-PSMA-617 will be used after androgen receptor directed therapy?** Due to the limited efficacy of rechallenging patients with an androgen receptor pathway inhibitor, currently only a single androgen receptor pathway inhibitor can be reimbursed by the NHS in the treatment pathway for prostate cancer.[7] The requirement of the VISION trial and expected indication is that patients would have failed at least one androgen receptor pathway inhibitor therapy, and thus would not be eligible to receive further androgen receptor pathway inhibitor treatment. androgen receptor pathway inhibitors therefore do not represent relevant comparators for ^{177}Lu-PSMA-617. **Subject to the ongoing NICE technology appraisal of olaparib [ID1640], would ^{177}Lu-PSMA-617 be used as a treatment option for the subgroup of people with BRCA1/2- mutations if a targeted treatment for this group such as olaparib was available?**	Comment noted. No action required. Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		The expected indication of ^{177}Lu-PSMA-617 is [redacted] It is expected that there would be a ~10% overlap in the patient populations who would be eligible to receive ^{177}Lu-PSMA-617 and olaparib (i.e., are both PSMA positive and express BCRA1/2). However, BCRA1/2 mutations were not measured or used as a stratification factor in the VISION study. **If a person had previously had off-label docetaxel in combination with ADT for treating hormone-sensitive prostate cancer and an ARDT is it anticipated that they would be eligible for treatment with ^{177}Lu-PSMA-617? Or, is it anticipated that ^{177}Lu-PSMA-617 would only be used after docetaxel, when docetaxel is used according to its marketing authorisation?** Patients who have received docetaxel in combination with ADT or an androgen receptor pathway inhibitor earlier in the treatment pathway would be eligible for treatment with ^{177}Lu-PSMA-617. However, it should be noted that these patients would not be expected to receive retreatment with docetaxel in the mCRPC setting.[6] It should be noted that docetaxel has been excluded as a comparator in previous NICE appraisal of treatments for mCRPC.[6] **Are the outcomes listed appropriate?** Please see comments in the 'Outcomes' row above.	Comment noted. See comparator section. No action required. Comment noted. See comparator section. No action required. Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		Are there any subgroups of people in whom 177Lu-PSMA-617 is expected to be more clinically effective and cost effective or other groups that should be examined separately? Please see comments in the 'Population' row above.	Comment noted. No action required.
		Where do you consider 177Lu-PSMA-617 will fit into the existing NICE pathway, Prostate cancer? In the existing NICE pathway for treatment of prostate cancer, ^{177}Lu PSMA-617 would be positioned under the 'treating hormone-relapsed metastatic prostate cancer' heading, as an option within the 'treatment options after chemotherapy with docetaxel regimen' box. It should be noted that in this pathway an androgen receptor pathway inhibitor and docetaxel could have been given earlier in treatment pathway. Additionally, patients may not be suitable or may decline to receive taxane-based chemotherapy. The anticipated licensed indication is [redacted] and therefore patients may also have received prior treatment with other taxane-based therapies, such as cabazitaxel	Comment noted. No action required.
		NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:	

Section	Consultee/ Commentator	Comments [sic]	Action
		• **could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which 177Lu-PSMA-617 will be licensed;** • **could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g., by making it more difficult in practice for a specific group to access the technology;** • **could have any adverse impact on people with a particular disability or disabilities.** **Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.**	
		Please see comments in the 'Equality' row above.	Comment noted. No action required.
		Do you consider 177Lu-PSMA-617 to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?	
		Please see comments in the 'Innovation' row above.	Comment noted. No action required.
		Do you consider that the use of ^{177}Lu-PSMA-617 can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?	
		The prolonged rPFS and OS for patients treated with ^{177}Lu-PSMA-617 has the potential to offer new hope to patients and improve their social, family, and emotional wellbeing. PRO measures (EQ-5D, FACT-P, BPI-SF) have been collected in the VISION trial.	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		^{177}Lu-PSMA-617 is administered every six weeks for up to a maximum of six cycles, and therefore this treatment may be more convenient for patients and healthcare systems than current SOC. **Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.** AAA continues to explore the scientific literature and real-world evidence sources to further substantiate benefits of treatment outside of that captured by the QALY measure for both patients and caregivers/family members. **To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.** Yes, there is currently not enough capacity in the NHS to deliver Lutetium-177 radioligand therapies. There are currently 23 centres in the UK who have a licence and appropriate capabilities to administer a similar therapy, ^{177}Lu oxodotreotide for the treatment of neuroendocrine tumours. These and potentially up to 41 additional new centres will be required to obtain an Administration of Radioactive Substances Advisory Committee (ARSAC) licence for the administration of ^{177}Lu-PSMA-617, as well as an Environmental Agency licence for the handling of Lutetium-177. Most importantly, in addition to these required licences, these centres require appropriately trained staff and rooms meeting specific radioprotection criteria for the delivery of therapy. The limited number of centres currently delivering Lutetium-177 therapy may have an impact on equal access to patients across the country as identified in	Comment noted. No changes required. Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		the “Equality” row above. Due to the need for appropriate licensing and resource planning, expansion or the setting up of a new Lutetium-177 service requires substantial planning. Through discussions with potential treatment centres, difficulties in securing budget for setting up new services have arisen as NHS will not approve budget for therapies which have not undergone a NICE appraisal. This may have a significant impact on the implementation of ^{177}Lu-PSMA-617 due to much higher prevalence of mCRPC compared to gastroenteropancreatic neuroendocrine tumours who are currently treated with 177-Lutetium therapy. The potential influx of mCRPC patients to these services could result in longer waiting lists and longer travel for some patients creating further inequality. Treatment centres may also prepare for ^{177}Lu-PSMA-617 by setting up private services in order to have the capability to treat patients sooner, generating further inequity in care according to private health insurance coverage or income levels. **NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process.** The company considers the STA process appropriate for the appraisal of ^{177}Lu-PSMA-617. References: 1. Food and Drugs Administration (FDA). FDA Approves First PSMA-Targeted PET Imaging Drug for Men with Prostate Cancer. Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-first-psma-targeted-pet-imaging-drug-men-prostate-cancer. [Last accessed: June 2021].	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		2. Mix M, Schultze-Seemann W, von Büren M, et al. 99mTc-labelled PSMA ligand for radio-guided surgery in nodal metastatic prostate cancer: proof of principle. EJNMMI Research 2021;11:22. 3. Maurer T, Robu S, Schottelius M, et al. 99mTechnetium-based Prostate-specific Membrane Antigen–radioguided Surgery in Recurrent Prostate Cancer. European Urology 2019;75:659-666. 4. Sartor O, de Bono J, Chi KN, et al. Lutetium-177–PSMA-617 for Metastatic Castration-Resistant Prostate Cancer. New England Journal of Medicine 2021. 5. National Prostate Cancer Audit. Annual report 2020. Available at: https://www.npca.org.uk/content/uploads/2021/01/NPCA-Annual-Report-2020_Final_140121.pdf [Last accessed: June 2021]. 6. National Institute for Health and Care Excellence (NICE). Olaparib for previously treated, hormone-relapsed metastatic prostate cancer with homologous recombination repair gene mutations [ID1640]. Available at: https://www.nice.org.uk/guidance/indevelopment/gid-ta10584. [Last accessed: June 2021]. 7. National Institute for Health and Care Excellence (NICE). Prostate cancer: diagnosis and management (NG131). Available at: https://www.nice.org.uk/guidance/ng131. [Last accessed: June 2021].	
	Bayer plc	Responses to the additional consultation questions are provided below. **Do you consider that the use of 177Lu-PSMA-617 can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?** The impact on the quality of life of the administration procedure (i.e. 30 min infusion with extended observation which could require patients to remain for	Comment noted. No action required.

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		a full day at the administration site, followed by restricted guidance on people contact and travel) may not be well captured in the QALY measure when derived using the EQ-5D instrument; nor is the impact on the quality of life of close contacts and carers of any spill over radiation effects.	
	Prostate Cancer UK	Responses to the additional consultation questions are provided below. The VISION trial was an international trial, including centres and investigators based in the UK. Lu-PSMA-617 continues to be available at the Royal Marsden NHS Foundation Trust and certain private providers in the UK. See the section on the proposed population for discussion of identifying PSMA-positive patients within the population. Different trials have used different definitions of PSMA positivity, including some with specified Standardised Uptake Values in PET scans. Comparators and established treatments are discussed above. Androgen receptor directed therapies, excluding those used as androgen deprivation therapy (ADT), are abiraterone, enzalutamide, apalutamide and darolutamide. It is appropriate not to consider these comparators as they will have been used earlier in the pathway, potentially in the metastatic hormone-sensitive setting (enzalutamide, potentially apalutamide) or the non-metastatic castrate-resistant setting (darolutamide, potentially apalutamide) and/or in the metastatic castrate-resistant setting prior to Lu-PSMA-617. There is no biological reason why PSMA-positive patients who are also BRCA1/2-positive could not be treated with both Lu-PSMA-617 and olaparib (or other PARP inhibitors). We are unaware of any trials of these therapies used in combination. The choice of treatment would be down to published survival benefit, patient suitability and clinical judgement. We would consider off-label use of docetaxel in the metastatic hormone-sensitive indication to meet the definition of previous treatment with taxane	Comments noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		chemotherapy. Therefore, patients who had received this treatment and an ARDT would be eligible for Lu-PSMA-617. As discussed above, data analysis using different definitions of PSMA positivity may reveal subgroups of patients for whom Lu-PSMA-617 would be more effective. The current positioning of Lu-PSMA-617 in the metastatic castrate-resistant indication after prior treatments to be determined is appropriate in the context of the NICE prostate cancer pathway given the current evidence base. We would note that other trials are currently under way testing the use of Lu-PSMA-617 earlier in the pathway and in combination with other therapies and these may result in further indications being submitted to NICE in future. There are potential barriers to adoption of this technology into practice. There are challenges in nuclear medicine capacity to deliver this treatment at the scale of the patient population. Investment would be required in staff (consultants in nuclear medicine and/or oncology, nurses, radiopharmacists, radiologists) and facilities (radiopharmacy, treatment and isolation rooms, radiation protection equipment). There would also be an increase in the radioactive waste produced by hospitals offering the treatment, which in some cases may breach existing environment agency certification. NHS England are aware of these barriers and are investigating the potential to tackle them, with the assistance of the manufacturer, Prostate Cancer UK, and the British Nuclear Medicine Society, among others.	
	Welsh Health Specialised Services Committee	Responses to the additional consultation questions are provided below. **Is prostate specific membrane antigen expression currently tested in UK clinical practice?**	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		No **How will people with PSMA-positive hormone relapsed metastatic prostate cancer be identified in clinical practice?** This could be done with PSMA PET scans. Currently there is variable access and funding for these across the UK. Within Wales PSMA PET scans are routinely commissioned for most patients with hormone relapsed metastatic prostate cancer. These indications (see below) are clearly defined in the WHSSC all Wales PET commissioning policy (CP50a): Prostate Cancer (18 F-Choline PET/CT or F-PSMA PET) • Staging of high risk patients (clinical T3 or above OR PSA > 20 OR Gleason 8 or above) who are considered potential candidates for curative treatment following conventional imaging. • Suspected recurrence in patients with a rapidly rising prostate-specific antigen (PSA) and negative or equivocal conventional imaging where the results would directly influence patient management PSMA PET scans are therefore not specifically commissioned for patients with hormone relapsed metastatic prostate cancer being considered for Lu-177 PSMA therapy.	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		However the majority of positive hormone relapsed metastatic prostate cancer patients have PSMA positive disease (>90%) so the cost benefit of this would need to be considered. Some trials require a FDG PET scan in addition to a PSMA PET scan to exclude patients with large volume PSMA-negative disease but the cost benefit and practicality of this would need to be considered. There are two main used PSMA imaging moieties: 68Ga-PSMA-11 and 18F-PSMA; Ga is thought to target the same part of PSMA as Lu177, but 18F is more widely available; the cost benefit and practicality of this would need to be considered **Is there a cut-off threshold of PSMA expression for being PSMA-positive?** No **Have all relevant comparators for 177Lu-PSMA-617 been included in the scope?** Yes **Which treatments are considered to be established clinical practice in the NHS for hormone relapsed metastatic prostate cancer previously treated with androgen receptor directed therapy (ARDT) and taxane based chemotherapy?**	Comment noted. No action required. Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		Re-challenge with taxane based chemotherapy (cabazitaxel if only docetaxel previously used, whether for hormone sensitive or hormone refractory disease; docetaxel if both docetaxel and cabazitaxel have previously been used) Ra223 if bone only disease and post-taxane and post-ARDT (any order and indication) OR post-ARDT and not fit for taxane chemotherapy. **How should best supportive care be defined?** • Clinical trials • Palliative external beam radiotherapy • Blood transfusions • Low dose dexamethasone **What treatments used in UK clinical practice are classed as androgen receptor directed therapies?** Abiraterone, enzalutamide, apalutamide and darolutamide; in practice most patients it will just be abiraterone and enzalutamide. **Is it appropriate to exclude abiraterone and enzalutamide as potential comparators because patients can only receive them once in UK clinical practice and it is expected that 177Lu-PSMA-617 will be used after androgen receptor directed therapy?**	Comment noted. See comparator section. No action required. Comment noted. No action required. Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		It is clear that standard international practice is delivery of both abiraterone and enzalutamide, despite low response rates; it is also likely to be the standard of care for future clinical trials	Comment noted. No action required.
		Subject to the ongoing NICE technology appraisal of olaparib [ID1640], would 177Lu-PSMA-617 be used as a treatment option for the subgroup of people with BRCA1/2- mutations if a targeted treatment for this group such as olaparib was available?	
		Yes – to our knowledge there is no evidence that Lu177 PSMA 617 is less effective in patients with BRCA1/2 mutated cancers and there may be more effect due to defective DNA damage recognition and repair and Lu177 mechanism of action (presumably causation of double stranded DNA breaks).	Comment noted. No action required.
		If a person had previously had off-label docetaxel in combination with ADT for treating hormone-sensitive prostate cancer and an ARDT is it anticipated that they would be eligible for treatment with 177Lu-PSMA-617? Or, is it anticipated that 177Lu-PSMA-617 would only be used after docetaxel, when docetaxel is used according to its marketing authorisation?	
		Yes, many patients will not want to ever be re-challenged with docetaxel having previously had it.	Comment noted. No action required.
		Are the outcomes listed appropriate? Yes	Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		Are there any subgroups of people in whom 177Lu-PSMA-617 is expected to be more clinically effective and cost effective or other groups that should be examined separately? Not to our knowledge **Where do you consider 177Lu-PSMA-617 will fit into the existing NICE pathway, Prostate cancer?** Based on VISION – after exposure to both ARDT and at least one taxane. **NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:** **• could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which 177Lu-PSMA-617 will be licensed;** **• could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;** **• could have any adverse impact on people with a particular disability or disabilities.**	Comment noted. No action required. Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		Their maybe inequity created by denying Lu177 PSMA to patients who are unfit for taxane chemotherapy equivalent to the Ra223 appraisal. **Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.** **Do you consider 177Lu-PSMA-617 to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?** Yes **Do you consider that the use of 177Lu-PSMA-617 can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?** No **Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.** **To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.** • Clinical services to deliver Lu177 PSMA are low in resilience. • Very few centres will have Lu177 PSMA ARSAC licenses • Very few clinicians will have Lu177 PSMA ARSAC licenses	Comment noted. No action required. Comment noted. No action required. Comment noted. No action required. Comment noted. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
Additional comments on the draft scope	Advanced Accelerator Applications (AAA), A Novartis Company	No additional comments.	Comment noted. No action required.
	Bayer plc	No comment	Comment noted. No action required.
	Prostate Cancer UK	No comment	Comment noted. No action required.
	Welsh Health Specialised Services Committee	Please note: the Welsh Health Specialised Services Committee consulted with urological cancer experts from across NHS Wales in order to prepare our response to the draft scope.	Comment noted. No action required.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

AstraZeneca UK